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Preliminary report

Effect of cyclosporine on lymphocytic variant hypereosinophilic syndrome

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ABSTRACT

Lymphocytic variant hypereosinophilic syndromes (L-HES) is thought to be caused by the over-production of interleukin (IL)-5 by type 2 helper cells, which leads to reactive eosinophil expansion and activation. Here we demonstrate the effect of cyclosporine in a patient with L-HES.
In the present case, the surface markers of cells from resected lymph nodes or peripheral blood were analyzed by flow cytometry. Serum concentrations of IL-4, IL-5, and IL-8 were measured using an enzyme-linked immunosorbent assay.
Methyl-prednisolone pulse therapy followed by the administration of 150 mg/day of cyclosporine combined with 15 mg/day of prednisolone ameliorated eosinophilia. However, abnormal CD3−CD4+ T cell clones remained even when the eosinophil count recovered to normal levels. An elevated IL-8 level was observed only when eosinophils increased. On the other hand, serum IL-4 and IL-5 levels were under detectable limits during the course.
Cyclosporine was effective in decreasing the eosinophil count without the elimination of abnormal T cell clones in the present case. Cytotoxic agents may be necessary to cure this serious disease. Moreover, target therapy for IL-8 may be a new strategy for L-HES with high IL-8 and low IL-5 concentrations.
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1. Introduction

Hypereosinophilic syndromes (HES) are defined by the presence of eosinophilia (>1500 eosinophils/mm^3 for at least 6 months) without a known cause, and evidence of organ dysfunction directly attributable to the eosinophilia. In addition, they have been distinguished from other eosinophilic disorders that are limited to certain organs, such as eosinophilic pneumonia, eosinophil-associated gastrointestinal disease, and eosinophilic cystitis [1]. The clinical heterogeneity of HES has been recognized with differing epidemiology, pathogenesis, and prognosis. HES was subcategorized into some categories such as "myeloproliferative variants (M-HES)", "lymphocytic variants (L-HES)", "familial eosinophilia", "undefined forms of HES", "overlap eosinophilic diseases", and "eosinophil-associated diseases" [2,3]. Two subtypes, in particular, have been well described. One is M-HES, most commonly by the fusion of the Fip1-like 1 (*FIP1L1*) gene and platelet-derived growth factor receptor-α (*PDGFRA*) gene due to a deletion or translocation of the *CHIC2* locus at chromosome 4q12[4,5]. Another is L-HES, in which the underlying cause of eosinophilia is the over-production of interleukin (IL)-5 by type 2 helper cells, leading to "reactive" eosinophil expansion and activation [6,7].

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Here we report a patient with L-HES whose symptoms were ameliorated by the administration of cyclosporine, but abnormal T cell clones remained even after the eosinophil count was decreased.

2. Materials and methods

2.1. Case presentation

A 60-year-old man was admitted to the hospital due to skin eruption, peripheral edema, and nasal obstruction. He had a history of treatment with interferon-α for type C hepatitis, and was complicated by depression due to interferon 7 years ago; however, he had no previous history of hematological or allergic diseases, and had not been administered any drugs implicated in eosinophilia.

Upon admission, he exhibited severe edema in the face, upper and lower extremities, and itchy eruptions on the whole body. The small lymph nodes (LNs) (5–10 mm in diameter) were swollen in the bilateral cervical and axillary regions.

Laboratory findings revealed WBC 14.1×10^9/l (neutrophils 42.7%, lymphocytes 11.6%, monocytes 4.6%, eosinophils 20.7%, and basophils 0.4%), without the expansion of abnormal lymphocytes, RBC 4.86×10^{12}/l, Hb 14.6 g/dl, and platelet count 252×10^9/l. Serum chemistry was normal except for lactic dehydrogenase (270 IU/l; normal, 106-211). His serum IgE level was slightly elevated (406 IU/ml; normal, <173), whereas thymus and activation-regulated chemokine (TARC, 282900 pg/ml; normal, <450), and soluble interleukin-2 receptor (sIL-2R, 5109 U/ml; normal, 145–519) were highly elevated.

Human T-cell leukemia virus type 1 (HTLV-1) was negative, and both the rate and score of neutrophil alkaline phosphatase were at the same levels as the control. Rheumatoid factor, anti-nuclear antibody, proteinase-3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA), and myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA) were negative. The causes of secondary eosinophilia were not observed, such as a parasitic infection, drugs, vasculitis, or allergic diseases.

Splenomegaly, apparent masses, or lymph node (LN) enlargement were not observed in the chest, abdominal, or intracranial areas by helical 16-slice computed tomography (SOMATOM®, Siemens Japan, Tokyo); however, the mucous membranes of the nasal cavity was severely swollen.

Biopsies of the nasal cavity revealed increased mucous glands and the infiltration of inflammatory cells containing lymphocytes and eosinophils without dysplasia. Granulomas, malignant cells, or vasculitis were not observed (data not shown).

Bone marrow biopsy/aspiration performed on the 2nd hospitalized day demonstrated normocellular marrow (nuclear cell count 7.5×10^4/μl, megakaryocytes 99/μl) with increased eosinophils (21.0%). Dysplasia was not observed in three lineages without the invasion of abnormal lymphocytes. Chromosomal analysis revealed a normal karyotype, and the deletion of chromosome 4q12 was not observed by fluorescence *in situ* hybridization analysis.

We performed cervical LN biopsy to rule out malignant lymphoma, although in the present case, only small surface LNs were detected. The histologic examination revealed a barely preserved follicular pattern (Fig. 1A,B) and diffuse infiltration of inflammatory cells containing small to large-sized lymphocytes and plasma cells (Fig. 1C,D). The expansion of eosinophils was observed in increased small vessels (Fig. 1D). An immunohistochemical study demonstrated that most lymphocytes were positive for CD4 (Fig. 1E), with only small populations of CD8+ T cells (Fig. 1F) or CD20+ B cells (Fig. 1G). Some CD4+ cells were CD3− (Fig. 1H). Chromosomal analysis revealed a normal karyotype. A small fraction of monoclonal T cell expansion cells was confirmed by a T cell receptor (TCR) rearrangement band demonstrated by Southern blot hybridization obtained from LN biopsy specimens (Fig. 2A). On the other hand, monoclonal B cell expansion was not observed by a negative IgH rearrangement band in LN cells (data not shown).

He was diagnosed as lymphocytic variant HES (L-HES). Methylprednisolone pulse therapy (1000 mg/day for 3 days) ameliorated both his symptoms and peripheral eosinophilia; however, he suffered from steroid psychosis, and eosinophils gradually increased again concomitant with the tapering of prednisolone [PSL]. Hydroxyurea (HU) partially decreased the eosinophil count; however, cyclophosphamide had no effect. Subsequent administration of 150 mg/day of cyclosporine combined with 15 mg/day of PSL ameliorated his eosinophilia, and he could leave the hospital (Fig. 2D). Seven weeks later, he was re-admitted to the hospital due to severe respiratory insufficiency and died of cytomegalovirus pneumonia. An autopsy was not performed.

2.2. Flow cytometric analysis

The surface markers of cells from resected lymph nodes or peripheral blood were analyzed by flow cytometry (SRL Co.). Since all CD8+ cells were positive for CD3 (Fig. 2B), CD4 cells were divided into CD3+CD4+ cells and CD3−CD4+ cells by the following calculation, although a two-color stain of CD3 and CD4 was not performed; [CD3+CD4+ cells] = [CD3+ cells] − [CD8+ cells], [CD3−CD4+ cells] = [CD4+ cells] − [CD3+CD4+ cells].

2.3. Cytokine investigation by enzyme-linked immunosorbent assay (ELISA)

With the patient's consent, serum was isolated and immediately stored at −80 °C. Serum concentrations of IL-4, IL-5, and IL-8 were measured using Human IL-4 ELISA Kit® (Invitorogen, Camarillo, CA), Human IL-5 ELISA Kit® (Invitorogen), and Human IL-8 ELISA Kit® (BioSource, Camarillo, CA), respectively.

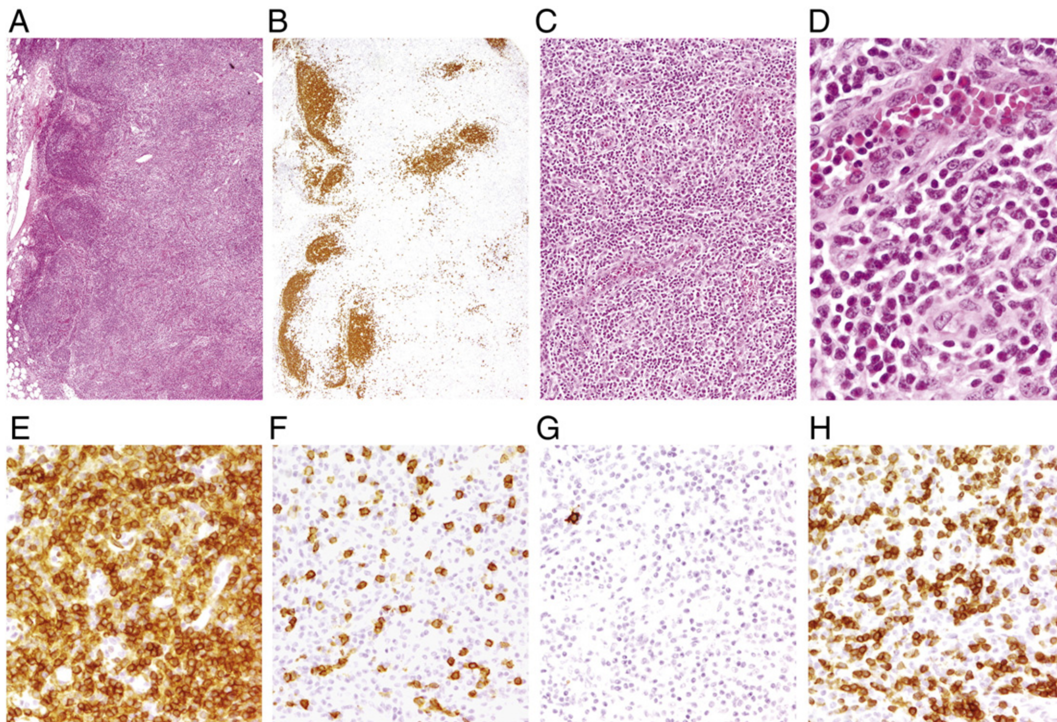

Fig. 1. Histological and immunohistochemical findings of resected lymph nodes. (A,B) On a low-power field, the follicular pattern of the LN was hardly preserved (A, HE ×2), which was shown by positive reactivity for CD20 (B, ×2) and the diffuse infiltration of inflammatory cells was observed. (C,D) Inflammatory cells contain small to large-sized lymphocytes and plasma cells (C, HE ×10; D, HE ×40). The expansion of eosinophils was observed in increased small vessels. (E–H) An immunohistochemical study demonstrated that most lymphocytes were positive for CD4 (E, ×40), with only small populations of CD8+ T cells (F, ×40) or CD20+ B cells (G, ×40). Some CD4+ cells were CD3− (H, ×40).

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